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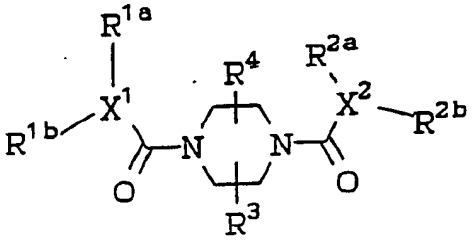

(I)

(57) Abstract

Diacylpiperazines of general structure (I) are: angiotensin II (A-II) antagonists selective for the type 2 (AT_2) subtype useful in the treatment of cerebrovascular, cognitive, and CNS disorders; tachykinin receptor antagonists useful in the treatment of inflammatory diseases and pain or migraine; and calcium channel blockers useful in the treatment of cardiovascular conditions such as angina, hypertension or ischemia.

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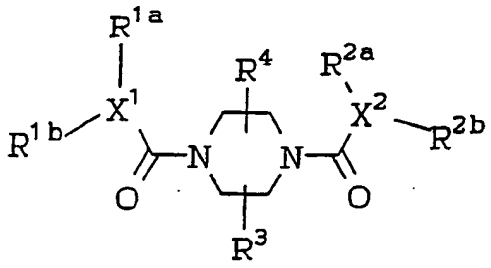
TITLE OF THE INVENTION

N,N-DIACYLPIPERAZINES

SUMMARY OF THE INVENTION

This application is a continuation-in-part of copending application Serial No. 07/703,953, filed May 22, 1991.

This invention is concerned with novel compounds represented by structural formula I:



I

wherein the X groups are generally N, CH or O and the R^1 and R^2 groups generally are alkyl, substituted alkyl phenyl or substituted phenyl.

The invention is also concerned with pharmaceutical formulations with these novel compounds as active ingredients and the use of the novel compounds and their formulations in the treatment of certain (CNS) disorders.

The compounds of this invention have central nervous system (CNS) activity and are useful in the treatment of cognitive dysfunctions including Alzheimer's disease, amnesia and senile dementia. These compounds also have anxiolytic and antidepressant properties and are, therefore, useful in the relief of symptoms of anxiety and tension and in the treatment of patients with depressed or dysphoric mental states.

In addition, these compounds exhibit antidopaminergic properties and are thus useful to treat disorders that involve dopamine dysfunction such as schizophrenia.

Furthermore, these compounds are tachykinin receptor antagonists and are useful in the treatment of inflammatory diseases and pain or migraine.

Also, these compounds are calcium channel blockers and are useful in the treatment of cardiovascular disorders such as angina, hypertension or ischemia.

BACKGROUND OF THE INVENTION

It is now known that there are two subtypes of angiotensin-II (A-II) receptors, the AT_1 and AT_2 subtypes. Recent studies have shown that in rat brain, A-II receptors are primarily of the AT_2 subtype [Chang et al., Biochem. Biophys. Res.

Commun., 171, 813 (1990)]. Agents acting as specific antagonists at these brain A-II receptors are of value in the treatment of a variety of cerebrovascular, cognitive and CNS disorders. For example, the utility of compounds having activity at the AT_2 receptor is disclosed by Bumpus, et al, Hypertension, 17, 720-721 (1991).

Receptors of the AT_2 subtype are also found in female reproductive organs of mammals, including uterus (Dudley, et al, Molecular Pharmacol., 38 370-377 (1990)) and ovaries (Pucell, et al, Endocrinology, 128, 1947-1959 (1991)). The role of angiotensin II in processes leading to ovulation has been reviewed (Andrade-Gordon, et al, Biochem. Pharmacol., 42, 715-719 (1991)).

In addition, AT_2 receptors are found in neuronal tumor cells (Speth, et al, Peptide Res., 2, 232-239 (1989)) and in transformed human neural cells (Tallant, et al, Hypertension, 17, 1135-1143 (1991)).

Some AT_2-selective A-II antagonists are known. See for example EP 245,637 and Chang et al., Mol. Pharmacol, 29, 347 (1990) which disclose compounds with structures somewhat different from those of the present application and of rather low potency. Also Whitebread et al., Biochem. Biophys. Res. Commun., 163, 284 (1989) describes a peptide with selective AT_2 antagonist properties but as with all peptides suffers rapid metabolic breakdown and lack of oral activity. Warner-Lambert PCT Patent Publication No. WO 92/05784 discloses certain AT_2-selective A-II antagonists as having a wide variety of utilities.

Some compounds of chemical structures somewhat similar to those of the compounds of the present invention have been reported in U.S. Patents 4,089,958 and 4,138,564. However, they are reported as chemical intermediates only.

Some 1,4-bis(diphenylacetyl)piperazines (without substituents on the piperazine ring carbons) have been disclosed as analgesic, antipyretic, and antiinflammatory agents and CNS depressants (U.S. Patent 3,288,795). The preparation of 1,4-bis(diphenylcarbamoyl)piperazine has been reported [D.E. Rivett and J.F.K. Wilshire, Australian J. Chem., 19, 165 (1966)]. Unsymmetrical 1-acyl-4-(diphenylcarbamoyl)piperazines and 1-acyl-4-(dialkylcarbamoyl)piperazines have also been described [L. Korzycka, et al., Pol. J. Pharmacol. Pharm., 38, 545 (1986); L. Toldy, et al., Acta. Chim. Acad. Sci. Hung., 70, 101 (1971)]. All of these are unsubstituted on the piperazine ring carbons.

Certain 1,4-diacylpiperazine-2-carboxylates and related derivatives in which at least one of the acyl groups is substituted benzoyl have been disclosed as platelet-activating factor antagonists (U.S. Patent 4,923,870 and European Patent Application EP 0,368,670). Methyl 4-(benzyloxy-carbonyl)-1-(tert-butoxycarbonyl)piperazine-2-carboxylate has been reported as an intermediate (EP 0,368,670), as has methyl 1-(benzyloxycarbonyl)-4-(tert-butoxycarbonyl)piperazine-2-carboxylate and the coresponding acid [C.F. Bigge, et al., Tetrahedron Lett., 30, 5193 (1989).

Analgesia has historically been achieved in the central nervous system by opiates and analogs which are addictive, and peripherically by cyclooxygenase inhibitors that have gastric side effects. Substance P antagonists induce analgesia both centrally and peripherially. In addition, substance P antagonists are inhibitory of neurogenic inflammation.

The neuropeptide receptors for substance P (neurokinin-1; NK-1) are widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes. This includes sensory perception of olfaction, vision, audition and pain, movement control, gastric motility, vasodilation, salivation, and micturition (B. Pernow, Pharmacol. Rev., 1983, 35, 85-141).

The receptor for substance P is a member of the superfamily of G protein-coupled receptors. This superfamily is an extremely diverse group of receptors in terms of activating ligands and biological functions. In addition to the tachykinin receptors, this receptor superfamily includes the opsins, the adrenergic receptors, the muscarinic receptors, the dopamine receptors, the serotonin receptors, a thyroid-stimulating hormone receptor, a luteinizing hormone-choriogonadotropic hormone receptor, the product of the oncogene mas, the yeast mating factor receptors, a Dictyostelium cAMP receptor, and receptors for other hormones and

neurotransmitters (see A.D. Hershey, et al., J. Biol. Chem., 1991, 226, 4366-4373).

Substance P (also called "SP" herein) is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The tachykinins are distinguished by a conserved carboxyl-terminal sequence Phe-X-Gly-Leu-Met-NH_2. In addition to SP the known mammalian tachykinins include neurokinin A and neurokinin B. The current nonmenclature designates the receptors for SP, neurokinin A, and neurokinin B as NK-1, NK-2, and NK-3, respectively.

More specifically, substance P is a pharmacologically-active neuropeptide that is produced in mammals and possesses a characteristic amino acid sequence that is illustrated below:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

(Chang et al., Nature New Biol. 232, 86 (1971); D.F. Veber et al., U.S. Patent No. 4,680,283).

Neurokinin A possesses the following amino acid sequence:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2.

Neurokinin B possesses the following amino acid sequence:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2.

Substance P acts as a vasodilator, a depressant, stimulates salivation and produces increased capillary permeability. It is also capable of producing both analgesia and hyperalgesia in

animals, depending on dose and pain responsiveness of the animal (see R.C.A. Frederickson et al., Science, 199, 1359 (1978); P. Oehme et al., Science, 208, 305 (1980)) and plays a role in sensory transmission and pain perception (T.M. Jessell, Advan. Biochem. Psychopharmacol. 28, 189 (1981)). For example, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510]. In particular, substance P has been shown to be involved in the transmission of pain in migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), and in arthritis (Levine et al. Science, (1984) 226 547-549). These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease, ulcerative colitis and Crohn's disease, etc. (see Mantyh et al., Neuroscience, 25 (3), 817-37 (1988) and D. Regoli in "Trends in Cluster Headache" Ed. F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, 1987, pp. 85-95).

It is also hypothesized that there is a neurogenic mechanism for arthritis in which substance P may play a role (Kidd et al., "A Neurogenic Mechanism for Symmetric Arthritis" in The Lancet, 11 November 1989 and Gronblad et al., "Neuropeptides in

Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10). Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis (O'Byrne et al., in Arthritis and Rheumatism (1990) 33 1023-8). Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions (Hamelet et al., Can. J. Pharmacol. Physiol. (1988) 66 1361-7), immunoregulation (Lotz et al., Science (1988) 241 1218-21, Kimball et al., J. Immunol. (1988) 141 (10) 3564-9 and A. Perianin, et al., Biochem. Biophys. Res. Commun. 161, 520 (1989)) vasodilation, bronchospasm, reflex or neuronal control of the viscera (Mantyh et al., PNAS (1988) 85 3235-9) and, possibly by arresting or slowing β-amyloid-mediated neurodegenerative changes (Yankner et al., Science, (1990) 250, 279-82) in senile dementia of the Alzheimer type, Alzheimer's disease and Downs Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press].

In the recent past, some attempts have been made to provide peptide-like substances that are antagonists for substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases listed above. See for example European patent applications (EPO Publication Nos. 0,347,802, 0,401,177 and 0,412,452) which disclose various peptides as neurokinin A

antagonists. Similarly, EPO Publication No. 0,336,230 discloses heptapeptides which are substance P antagonists useful in the treatment of asthma. Merck U.S. Patent No. 4,680,283 also discloses peptidal analogs of substance P.

Certain inhibitors of tachykinins have been described in U.S. Patent No. 4,501,733, by replacing residues in substance P sequence by Trp residues.

A further class of tachykinin receptor antagonists, comprising a monomeric or dimeric hexa- or heptapeptide unit in linear or cyclic form, is described in GB-A-2216529.

The peptide-like nature of such substances make them too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, as they are expected to be more stable from a metabolic point of view than the previously-discussed agents.

It is known in the art that baclofen (ß-(aminoethyl)-4-chlorobenzenepropanoic acid) in the central nervous system effectively blocks the excitatory activity of substance P, but because in many areas the excitatory responses to other compounds such as acetylcholine and glutamate are inhibited as well, baclofen is not considered a specific substance P antagonist. Pfizer WIPO patent applications (PCT Publication Nos. WO 90/05525 and WO 90/05729) and publications (Science, 251, 435-437 (1991); Science, 251, 437-439 (1991)) disclose 2-arylmethyl-3-substituted amino-quinuclidine

derivatives which are which are disclosed as being useful as substance P antagonists for treating gastrointestinal disorders, central nervous system disorders, inflammatory diseases and pain or migraine. A Glaxo European patent application (EPO Publication No. 0,360,390) discloses various spirolactam-substituted amino acids and peptides which are antagonists or agonists of substance P. A Pfizer WIPO patent application (PCT Publication No. WO 92/06079) discloses fused-ring analogs of nitrogen-containing nonaromatic heterocycles as useful for the treatment of diseases mediated by an excess of substance P.

Calcium channel blocking agents are a known group of drugs which act to inhibit transfer of calcium ions across the plasma membrane of cells. It is known that the influx of calcium ions into certain cells in the mammalian body, including the vascular smooth muscle cells and myocardial cells, participates in the activity of such cells and that the administration of calcium channel blockers (also known as calcium antagonists or calcium entry blockers), which inhibit such influx, would suppress myocardial contractile force and rate and cause vasodilation. Calcium channel blockers delay or prevent the cardiac contracture which is believed to be caused by an accumulation of intracellular calcium under ischemic conditions. Calcium overload, during ischemia, can have a number of additional adverse effects which would further compromise the ischemic myocardium. These include less efficient use of oxygen for ATP production, activation of

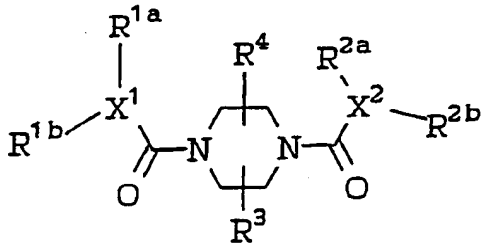
mitochondrial fatty acid oxidation, and possibly, promotion of cell necrosis. Calcium channel blockers are, therefore, useful in the treatment or prevention of a variety of diseases and disorders of the heart and vascular system, such as angina pectoris, myocardial infarction, cardiac arrhythmia, cardiac hypertrophy, coronary vasospasm, hypertension, cerebrovascular spasm and other ischemic disease. In addition, certain calcium channel blocking agents are capable of lowering elevated intraocular pressure when administered topically to the hypertensive eye in solution in a suitable ophthalmic vehicle.

Also, certain calcium channel blockers sensitize multidrug resistant cells to certain chemotherapeutic agents and are useful in the reversal of multidrug resistance by enhancing the efficacy of various anticancer agents (J. Biol. Chem., 262 (5), 2166-2170 (1987); Scientific American, 44-51 (March 1989)). In addition, certain calcium channel blockers are suggested as having activity in blocking calcium channels in insect brain membranes and so are useful as insecticides (EMBO J., 8(8), 2365-2371 (1989)).

A number of compounds having calcium channel blocking activity are known, for example certain dihydropyridine derivatives, such as nifedipine and nicardipine, and other compounds such as verapamil, diltiazem and flunarizine.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by structural formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is

1) H,
2) C_{1-8} alkyl,
3) phenyl, either unsubstituted or substituted with one or two substitutents selected from:
   a) $-C_{1-4}$ alkyl,
   b) -halo,
   e) -OH,
   d) $-CF_3$
   e) $-NH_2$,
   f) $-NH(C_{1-4}$ alkyl),
   g) $-N(C_{1-4}$ alkyl$)_2$,
   h) $-CO_2H$,
   i) $-CO_2(C_{1-4}$ alkyl), and
   j) $-C_{1-4}$ alkoxy; or

4) C_{1-4} alkyl-phenyl, wherein the phenyl is either unsubstituted or substituted with one or two substitutents selected from:
   a) $-C_{1-4}$ alkyl,
   b) -halo,
   e) -OH,
   d) $-CF_3$
   e) $-NH_2$,
   f) $-NH(C_{1-4}$ alkyl),
   g) $-N(C_{1-4}$ alkyl$)_2$,
   h) $-CO_2H$,
   i) $-CO_2(C_{1-4}$ alkyl), and
   j) $-C_{1-4}$ alkoxy;

R^{1b} is
1) R^{1a},
2) $-C_{3-7}$ cycloalkyl, or
3) $-CH_2-R^{1a}$;

R^{2a} and R^{2b} are independently phenyl, either unsubstituted or substituted with one or two substitutents selected from:
1) $-C_{1-4}$ alkoxy,
2) -halo,
3) -OH,
4) $-CF_3$
5) $-NH_2$,
6) $-NH(C_{1-4}$ alkyl),
7) $-N(C_{1-4}$ alkyl$)_2$,
8) $-CO_2H$,
9) $-CO_2(C_{1-4}$ alkyl), and

10) $-C_{1-6}$ alkyl, either unsubstituted or substituted with:
   a) -halo,
   b) -OH,
   c) $-CF_3$
   d) $-NH_2$,
   e) $-NH(C_{1-4}$ alkyl),
   f) $-N(C_{1-4}$ alkyl$)_2$,
   g) $-CO_2H$,
   h) $-CO_2(C_{1-4}$ alkyl),
   i) C_{1-4}alkoxy,
   j) $-S(O)_x(C_{1-4}$ alkyl) wherein x is 0, 1 or 2,
   k) $-C_{3-7}$ cycloalkyl;

and the phenyl groups of R^{2a} and R^{2b} may be joined together at the ortho carbon atoms through a carbon-carbon single bond or C_{1-3} alkylene to form a tricyclic group with the X^2 to which they are attached;

X^1 is -N, -CH or O, and if X^1 is O, R^{1a} is absent;

X^2 is -N or -CH;

R^3 is
   1) $-C_{1-4}$ alkyl,
   2) $-CO_2R^6$,
   3) $-CH_2OCOR^6$,
   4) $-CH_2OH$,
   5) $-CH_2OR^5$,
   6) $-CH_2S(O)_xR^5$,

7) $-CH_2OCONR^5R^6$,
8) $-CH_2CONR^5R^6$,
9) $-CONR^5R^6$,
10) $-CO_2R^8$,
11) $-CH_2CO_2R^6$,
12) $-CH_2CO_2R^8$,
13) $-CONHSO_2R^9$
14) $-CH_2N(R^6)CONR^5R^6$,
15) $-CH_2NH_2$,
16) $-CH_2NH(C_{1-4}$ alkyl), or
17) $-CH_2N(C_{1-4}$ alkyl$)_2$; wherein

R^5 is C_{1-6} alkyl either unsubstituted or substituted with:

1) -halo,
2) -OH,
3) $-CF_3$,
4) $-NH_2$,
5) $-NH(C_{1-4}$ alkyl),
6) $-N(C_{1-4}$ alkyl$)_2$,
7) $-CO_2H$,
8) $-CO_2(C_{1-4}$ alkyl),
9) $-C_{3-7}$ cycloalkyl, or
10) phenyl, either unsubstituted or substituted with
   a) $-C_{1-4}$ alkyl,
   b) -halo,
   c) -OH,
   d) $-CF_3$
   e) $-NH_2$,
   f) $-NH(C_{1-4}$ alkyl),
   g) $-N(C_{1-4}$ alkyl$)_2$,

h) $-CO_2H$, or
i) $-CO_2(C_{1-4}$ alkyl);

R^6 is -H or C_{1-4} alkyl; or
R^5 and R^6 can be joined together to form with the nitrogen to which they are attached $-N(CH_2CH_2)_2L$; wherein L is:

i) a single bond,
ii) $-CH_2-$,
iii) -O-,
iv) $-S(O)_p-$, or
v) $-NR^7$;

R^7 is

1) -H,
2) $-C_{1-6}$alkyl, unsubstituted or substituted with -OH, $-C_{1-4}$ alkoxy or $-N(C_{1-4}alkyl)_2$,
3) -aryl, or
4) $-CH_2$-aryl;

R^8 is

1) -H,
2) $-\overset{R^7}{\underset{|}{C}}HOCOR^{10}$, wherein R^{10} is
   a) $-C_{1-6}$alkyl,
   b) -aryl, or
   c) $-CH_2$-aryl,
3) $-CH_2$-aryl,

R^9 is

1) -aryl,
2) -heteroaryl,
3) $-C_{3-7}$cycloalkyl,

4) -polyfluoro-C_{1-4}alkyl
5) -C_{1-6}alkyl, either unsubstituted or substituted with
   a) -aryl,
   b) -heteroaryl,
   c) -OH,
   d) -SH,
   e) -C_{1-4}alkyl,
   f) -C_{3-7}cycloalkyl,
   g) -C_{1-4}alkoxy,
   h) -C_{1-4}alkylthio,
   i) -CF_3,
   j) -halo,
   k) -NO_2,
   l) -CO_2R^6
   m) -$N(R^6)_2$, wherein the R^6 groups are the same or different,
   n) -NH-aryl,
   o) -$N(aryl)_2$,
   p) -PO_3H,
   q) -$PO(OH)(OC_{1-4}alkyl)$ or
   r) -$N(CH_2CH_2)_2L$ wherein L is as defined above, and

R^4 is H or R^3.

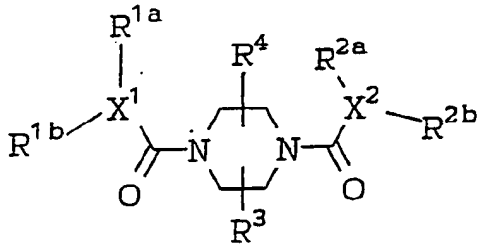
The term "aryl" means phenyl or naphthyl either unsubstituted or substituted with one, two or three substituents selected from the group consisting of halo, C_{1-4}-alkyl, C_{1-4}-alkoxy, NO_2, CF_3, C_{1-4}-alkylthio, OH, $-N(R^6)_2$, $-CO_2R^6$, C_{1-4}-perfluoroalkyl, C_{3-6}-perfluorocycloalkyl, and tetrazol-5-yl.

The term "heteroaryl" means an unsubstituted, monosubstituted or disubstituted five or six membered aromatic heterocycle comprising from 1 to 3 heteroatoms selected from the group consisting of O, N and S and wherein the substituents are members selected from the group consisting of -OH, -SH, $-C_{1-4}$-alkyl, $-C_{1-4}$-alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2R^6$, $-N(R^6)_2$ and a fused benzo group;

The term "halo" means -Cl, -Br, -I or -F.

The term "alkyl", "alkenyl", "alkynyl" and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl.

For the antagonism of a tachykinin receptor, preferred compounds are those represented by structural formula II:



II

or a pharmaceutically acceptable salt thereof, wherein: